Chronic pain: the role of biological and psychosocial factors

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CHAPTER 8

SUMMARY AND GENERAL DISCUSSION

SUMMARY OF THE MAIN FINDINGS

Chronic pain is common and its contribution to the worldwide disease burden will continue to increase[1]. Mechanisms underlying the condition are still largely unknown. Chronic pain is hypothesized to be the consequence of central sensitization, hypersensitivity of neural nociceptive pathways ('pain pathways')[2]. Both biological factors and psychosocial factors are thought to contribute to central sensitization. Therefore, the overarching aim of this thesis was to examine biological factors, by themselves or in interaction with psychosocial factors, in relation to the onset and persistence of chronic pain. Our first aim of this thesis was to examine whether function of the hypothalamic-pituitary-adrenal axis (HPA axis) and the immune system (IMS) was associated with the presence and severity of chronic pain. Second, we tested whether function of biological stress systems (the HPA axis, IMS and the autonomic nervous system (ANS)), adverse life events, or a combination were associated with the onset and remission of chronic pain. Third, we examined whether the brain-derived neurotrophic factor (BDNF) pathway (val^{66}met genotype, gene expression and serum level), life events/trauma, or a combination were associated with the presence and severity of chronic pain. Fourth, we examined whether sleep disturbances were associated with the onset of chronic pain, and whether this effect was dependent on depressive symptoms. For all these studies, we used data from the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study which recruited 2981 persons, aged 18 through 65 years[3]. Chronic pain was defined as pain in the extremities, the back and the neck in the prior 6 months ('chronic multi-site musculoskeletal pain'). In the current chapter, the main findings of Chapter 2 through 7 will be summarized. First, we will discuss our main aims and main results as reported in each chapter of this thesis, followed by discussion of the main findings in relation to previous research. Furthermore, we will elaborate on methodological considerations, a clinical implication and suggestions for future research. The chapter finishes with an overall conclusion.

Table 1. Main results of chapter 2 through chapter 7 in this thesis.

	Cross-sectional studies		**Longitudinal studies**	
	Chronic pain presence	Chronic pain severity	Chronic pain onset	Chronic pain remission
Biological stress systems				
Autonomic nervous system	No associations [1]	Lower heart rate variability is associated with increased pain intensity [1]	No associations (ch. 4)	No associations (ch. 5)
HPA axis	Lower morning cortisol levels and a blunted diurnal slope in chronic pain subjects without depression and/or anxiety (ch. 2)	No associations (ch. 2)	No associations (ch. 4)	No associations (ch. 5)
Immune system	Unaltered basal inflammatory markers but increased innate immune response in chronic pain (ch. 3)	No associations (ch. 3)	No associations (ch. 4)	No associations (ch. 5)
Biological stress*events	N.E.	N.E.	No associations (ch. 4)	No associations (ch. 5)
Brain-derived neurotrophic factor				
BDNF	Unaltered BDNF serum and BDNF expression levels but altered genotype of the $Val^{66}Met$ polymorphism in chronic pain subjects (ch. 6)	No associations (ch. 6)	N.E.	N.E.
BDNF* events/trauma	No associations (ch. 6)	No associations (ch. 6)	N.E.	N.E.
Psychosocial stress				
Recent adverse life events	Increased number of adverse life events is associated with chronic pain presence (ch. 6)	Increased number of adverse life events is associated with higher pain intensity and disability within chronic pain group (ch. 6)	Increased number of adverse life events is associated with a higher risk of chronic pain onset (ch. 4)	No associations (ch. 5)
Childhood trauma	Increased level of childhood trauma is associated with chronic pain presence (ch. 6)	Increased childhood trauma is associated with higher pain intensity and disability within chronic pain group (ch. 6)	N.E.	N.E.
Sleep/depressive symptoms				
Insomnia Sleep duration	N.E.	N.E.	Insomnia and short sleep duration increase the risk of chronic pain onset, partially mediated by depressive symptoms (ch. 7)	N.E.
Depressive symptoms	N.E., although there seems to be a close link.[2] In this thesis, depression appeared as a relevant confounder/ moderator (ch. 2/3/6) and depressive symptoms as a partial mediator (ch. 7).	N.E., although significant associations have previously been found [2]	Depressive symptoms at baseline and a further increase in depressive symptoms over time are independently associated with a higher risk of chronic pain onset (ch. 7)	N.E.

[1] The cross-sectional association between the autonomic nervous system and chronic pain was examined in a previous NESDA study (Barakat et al.:[4]). [2] One previous NESDA study showed that individuals who reported any pain (back, neck, joint, facial, abdominal, head or chest pain) in the prior 6 months had higher levels of depressive symptoms. Also, the score of depressive symptoms was positively associated with an increased number of pain locations (Ligthart et al.: [5]).;

ch. = chapter; N.E. = not examined; * = in interaction with.

Biological stress systems, psychosocial stress and chronic pain

Results from each of the thesis chapters are summarized in Table 1. The hypothesis that we addressed in chapter 2-5 was that altered function of three biological stress systems –the HPA axis, IMS and ANS– induce and perpetuate central sensitization, an effect which is aggravated by the experience of adverse life events[6]. Our first step was to cross-sectionally examine whether these biological stress systems were associated with the presence and severity of chronic pain. One previous NESDA study examined function of the autonomic nervous system in relation to chronic pain[4]. In that study, no associations were found with the presence of chronic pain, although lower heart rate variability was associated with increased pain intensity among chronic pain subjects[4].

In **Chapter 2**, we focused on the question whether function of the HPA axis was cross-sectionally associated with the presence and severity of chronic pain. We compared salivary cortisol levels (awakening level, 1-hour awakening response, evening level, diurnal slope and postdexamethasone level) of persons with chronic pain (n=654) to a control group without chronic pain (n=471). We found that the chronic pain subjects showed lower cortisol level at awakening, lower evening level and a blunted diurnal slope compared to controls. However, lower cortisol level at awakening and a blunted diurnal slope appeared to be restricted to those without depressive and/or anxiety disorders, who also showed a lower 1-hour awakening response. Cortisol levels were not associated with pain severity among chronic pain subjects. Our findings suggest hypocortisolemia in chronic pain, which could be the result of a long-term underlying hyperactivity of the HPA axis due to prolonged stress exposure, which ultimately resulted in exhaustion of the system[7]. If chronic pain was accompanied by a depressive and/or anxiety disorder, the association between cortisol and chronic pain appears to be partly masked. This concurs with the notion that depression and anxiety are typically related to increased levels of cortisol[8-11]. Our findings mark the importance of taking into account psycho-pathology when examining HPA axis function in chronic pain, because depression/anxiety clearly modify this association.

In **Chapter 3**, we examined whether function of the IMS was cross-sectionally associated with the presence and severity of chronic pain. We compared blood levels of basal inflammatory markers and the innate immune response for subjects with chronic pain (n=754) to a control group without chronic pain (n=878). Basal inflammatory markers included C-reactive protein, interleukin-6, and tumor necrosis factor-alpha. The innate immune response was obtained by measuring levels of 13 inflammatory markers after lipopolysaccharide (LPS) stimulation in a subsample (n=707). Chronic pain subjects demonstrated higher levels of basal inflammatory markers compared to controls, but

statistical significance was lost after adjustment for lifestyle and disease variables. In particular, body mass index and chronic disease appeared to explain the association of basal inflammation with chronic pain. Chronic pain subjects did show increased levels of some LPS-stimulated inflammatory markers (4 out of 13), even after adjustment for lifestyle and disease variables. Pain severity was not associated with basal inflammation and the innate immune response among chronic pain subjects. Our findings suggest that lifestyle and disease variables should be taken into account as potential confounders when examining immune function in chronic pain. These variables might particularly influence levels of basal inflammatory markers because they strongly fluctuate within individuals, whereas the innate immune response seems to be more robust and under genetic control[12]. Moreover, our study found suggestive evidence for an increased innate immune response in chronic pain, which could be investigated as a risk factor for the onset or persistence of chronic pain.

In **Chapter 4**, we hypothesized that biological stress systems (HPA axis, IMS and ANS function), recent (<6 months) adverse life events, or a combination were longitudinally associated with the onset of chronic pain over 6 years follow-up. In subjects free from chronic pain at baseline (n=2039), we determined baseline HPA axis, IMS and ANS function, and the total number of recent adverse life events at baseline. Function of the HPA axis included assessment of salivary cortisol levels (awakening level, 1-hour awakening response, evening level, diurnal slope and postdexamethasone level). For function of IMS, both levels of basal inflammatory markers and the innate immune response were determined. Both sympathetic and parasympathetic activity of the ANS were examined. We followed-up our subjects for the onset of chronic pain after 2, 4 and 6 years. Our study could not confirm that function of biological stress systems (HPA axis, IMS and ANS) was associated with the onset of chronic pain, either by itself or in interaction with adverse life events. This potentially suggests that biological alterations in chronic pain subjects, as indicated by hypocortisolemia (Chapter 2) and an increased innate immune response (Chapter 3), are consequences rather than risk factors for developing chronic pain. We did find that an increased number of adverse life events was a risk factor for the onset of chronic pain. With the experience of every additional adverse life event, the risk of developing chronic pain over 6 years increased by approximately 14%. This finding may suggest that psychosocial factors play a role in triggering the development of chronic pain.

Chapter 5 aimed to test the hypothesis that function of biological stress systems (HPA axis, IMS and ANS), recent adverse life events, or a combination were longitudinally associated with the remission of chronic pain over 6 years follow-up. In subjects with chronic pain at baseline (n=665), we assessed baseline HPA axis, IMS and ANS function, and the total number of recent (<6 months) adverse life

events at baseline and 2-year follow-up. Function of the HPA axis included assessment of salivary cortisol levels (awakening level, 1-hour awakening response, evening level, diurnal slope and postdexamethasone level). IMS function was assessed by determining levels of basal inflammatory markers and the innate immune response. We examined both sympathetic and parasympathetic activity of the ANS. We followed-up our subjects for the remission of chronic pain after 2, 4 and 6 years. Our analyses showed that biological stress systems function and adverse life events were not associated with the remission of chronic pain, either as a main effect or in interaction. Thus, altered biological stress systems function and adverse life events do not seem to hamper the remission of chronic pain, neither cause its persistence. This suggests that other factors should be considered to be able to identify those with persisting chronic pain.

Brain-derived neurotropic factor, psychosocial stress and chronic pain

Another biological factor that may be involved in central sensitization is brain-derived neurotrophic factor (BDNF), a neurotransmitter involved in the growth and protection of neural pain pathways [6,13]. Psychosocial stress, such as adverse life events and childhood trauma, might aggravate the impact of BDNF on chronic pain[6].

In **Chapter 6**, we tested the hypothesis that BDNF, recent adverse life events/childhood trauma, or a combination were cross-sectionally associated with the presence and severity of chronic pain (n=1646). The complete BDNF pathway was examined (val^{66}met genotype, gene expression and serum level). Our analyses revealed that the BDNF val^{66}met polymorphism was associated with the presence of chronic pain. Specifically, carriers of the met allele were more likely to have chronic pain compared to val/val carriers. BDNF gene expression and serum levels were not associated with the presence of chronic pain. This suggests that the BDNF gene has no simple one-to-one mapping to peripheral levels. A possible explanation is that peripheral BDNF levels are influenced by other (genetic, environmental or biological) factors than the BDNF gene. We observed no associations for the BDNF pathway with pain severity among chronic pain subjects. Life stress did not aggravate the impact of BDNF on pain, but was rather directly associated with the presence and severity of chronic pain. Our results imply that the BDNF met allele could mark vulnerability for chronic pain, whereas BDNF gene expression and serum level do not seem to play a role in chronic pain. Subjects with chronic pain did report increased levels of recent adverse life events and childhood trauma, which underlines the relevance of examining the role of psychosocial factors in chronic pain.

Sleep disturbances, depressive symptoms and chronic pain

Disturbed sleep is another factor that is hypothesized to contribute to the development of chronic pain, and this effect is possibly mediated by the experience of depressive symptoms[14].

In Chapter 7, our focus was to study the longitudinal association of sleep disturbances at baseline with chronic pain onset over 6 years follow-up. In subjects free of chronic pain at baseline (n=1860), we examined whether insomnia and sleep duration predicted the onset of chronic pain, and whether this association was mediated by depressive symptoms. Depressive symptoms were assessed at baseline and as a change score over time (from baseline to the moment of chronic pain onset/censoring). We found that both short sleep duration (≤6 hours vs. 7-9 hours) and insomnia increased the risk of the onset of chronic pain. The association between sleep disturbances and chronic pain onset seemed to be partially mediated by depressive symptoms (ΔB=16-40%). In addition, baseline depressive symptoms and a further increase in depressive symptoms over time independently predicted chronic pain onset. Thus, insomnia, short sleep duration and depressive symptoms are all independent risk factors for developing chronic pain. This suggests it may be beneficial to improve sleep (quantity and quality) and depressive symptoms in order to decrease the risk of developing chronic pain.

DISCUSSION OF THE MAIN FINDINGS

Biological stress – cause or consequence of chronic pain?

Chronic pain subjects showed unaltered ANS function in one previous NESDA study[4]. Chronic pain subjects do seem to show altered function of the HPA axis and IMS, indicated by hypocortisolemia and an increased innate immune response in our cross-sectional studies (Chapter 2 and Chapter 3). However, altered function of the HPA axis, IMS and ANS was no risk factor for future onset of chronic pain (Chapter 4).

Thus, we could not confirm that biological vulnerability of the HPA axis, IMS and ANS predicts the development of chronic pain. What is the support of this notion from previous research? The general idea that changes in HPA axis, IMS and ANS predispose the development of chronic pain is based on a prominent hypothesis in the field[6]. However, most evidence for the involvement of biological stress systems comes from cross-sectional studies. A major caveat of these studies is that conclusions regarding causality cannot be drawn. In these studies, chronic pain subjects demonstrated altered sympathetic/parasympathetic balance, neuroendocrine and immune disturbances[6,15-17], and worsening of pain symptoms with the experience of stress[18-20]. Based on these findings, Maletic and Raison suggest a combination of biological and environmental underpinnings for chronic pain[6]. One previous longitudinal study (n=241) is a notable exception, which showed that altered function of the HPA axis predicted the onset of chronic widespread pain over 15 months follow-up[21]. Why

did they find their subjects to indicate biological vulnerability for chronic pain, whereas this was not confirmed in the NESDA study? This might be explained by measurement differences, e.g. in the assessment of pain, depression, anxiety and cortisol. In addition, the study by McBeth et al. followed-up their subjects over a shorter period (15 months) than our study (2, 4 and 6 years). Perhaps HPA axis changes can only induce chronic pain within a shorter time span than two years. On the other hand, HPA axis vulnerability might in particular develop early in life by adverse childhood experiences [22,23] or by prenatal factors[24]. This vulnerability is thought to subsequently lead to long-term brain alterations which may facilitate disease later on in life[25]. Thus, HPA axis vulnerability resulting in chronic pain seems to be a gradual rather than a short-term process. Another explanation for our distinct findings is heterogeneity of samples. McBeth et al. included a group with high rates of psychosocial stress based on somatic symptoms and illness behavior, whereas the NESDA study included a group with high rates of depression and anxiety. It could therefore be that subjects in the McBeth study were more vulnerable to HPA axis changes. Also, their participants may differ from our participants in the presence of comorbidities. For example, both studies have no information on post-traumatic stress disorder, even though it has previously been related to hypocortisolemia [16,26]. In addition, there are several methodological considerations that can explain our findings. This thesis found small to moderate cross-sectional associations for altered biological function with chronic pain, and these may not hold in subsequent longitudinal analyses with a smaller sample size. Another consideration is that most of our subjects already reported some pain at baseline. We cannot be completely sure that we predicted onset and remission of chronic pain rather than simply moving in and out of criteria of chronic pain. However, similar to the McBeth study, we checked the influence of pain intensity at baseline and this did not appear to affect our findings. Nevertheless, it is still possible that the transition from an absolutely pain-free state into a severe widespread pain state would result in different findings for biological stress systems with chronic pain. An important strength of our study, is that we have a much larger sample size (n=2039) than the McBeth study (n=241). Thus, we could also argue that if cortisol changes would predict the onset of chronic pain, we should have been able to shown this in our much larger cohort study.

Irrespective of the aforementioned considerations, our findings may also imply that biological alterations in chronic pain subjects are consequences rather than risk factors of the condition. Although we did not examine this in our study, it could be that chronic pain itself, by acting as a chronic stressor, is the cause of biological alterations at a later stage[27]. Our cross-sectional studies showed that these biological changes included hypocortisolemia and an increased innate immune response. Several previous studies also reported a hypoactive state of the HPA axis in chronic pain[6,16,21,28-30]. In acute pain, higher levels of cortisol are secreted be able to cope with the defense reactions

that are activated in response to stress. However, in case of chronic pain, the stress system may reach a state of exhaustion and the HPA axis turns to a state of hypoactivity[31]. Hypocortisolemia might be indicative of adrenal sufficiency, or disturbances at higher levels of the HPA axis, such as reduced secretion of corticotropin-releasing hormone from the hypothalamus[21,32,33]. In our study, hypocortisolemia seems to occur at awakening rather than in the evening. A possible explanation is a decreased cortisol secretion during the late phase of sleep or differences in frequency of cortisol peaks overnight[34,35]. This would concur with the finding that chronic pain subjects frequently suffer from sleep problems[36,37]. However, we did not measure nocturnal cortisol levels neither cortisol levels further throughout the day so this remains to be elucidated in future research. In this thesis, we also found suggestive evidence for an increased innate immune response in chronic pain. This might indicate a disturbed innate capacity of the IMS to produce cytokines. This could be the consequence of the prolonged incoming pain signals and the sustained inflammatory state[38]. Although hypocortisolemia and innate immunity likely play a role in chronic pain, the complete understanding of underlying processes remains to be elucidated.

Our study was the first large-scale longitudinal study to shed light on the role of three major biological stress systems in the etiology of chronic pain. In sum, we found altered function of biological stress systems in our cross-sectional studies, indicated by hypocortisolemia and an enhanced innate immune response, but these biological changes were no risk factor for the development of chronic pain.

How does psychosocial stress result in chronic pain?

Our finding that psychosocial stressors are related to the presence and severity of chronic pain seems to concur with several previous studies[39,40]. Specifically, our cross-sectional data demonstrated that chronic pain subjects report higher levels of recent adverse life events and childhood trauma (Chapter 6). Our longitudinal study confirmed that adverse life events were also prospectively involved in chronic pain (Chapter 4), which suggests that psychosocial factors may trigger the development of chronic pain. Our study is in line with several previous prospective studies that found recent life events and childhood trauma to increase the risk of developing chronic pain[41-43].

The effect between adverse life events and chronic pain onset was not modulated by biological stress systems, suggesting that another pathway should explain this link. Our study assessed baseline function of biological stress systems. Perhaps changes in biological stress systems over time can modulate between psychosocial stress and the onset of chronic pain, but this has not yet been examined. Also, it is possible that not basal activity of biological stress systems, but rather disturbed reactivity of biological stress systems (in response to a stressor) explains the link between life events

and chronic pain. Severe early life stress such as childhood trauma has been suggested to permanently alter HPA axis responses under challenge[25]. For example, patients with fibromyalgia have previously shown reduced cortisol release in response to a social stressor[26] or pharmacological challenge [44,45]. However, these studies had small sample sizes, and therefore future studies should examine the reactivity of biological stress systems in chronic pain in larger groups.

An alternative explanation is that psychosocial stressors directly trigger central sensitization, without modulation of biological stress systems. Experiences or environmental triggers have been suggested to play a role in the transition from acute pain to chronic pain[46]. Psychosocial factors that are thought to affect the experience of pain include cognitions (i.e. thoughts, beliefs and appraisals), coping responses and social environmental variables[47]. Cognitions can be seen as nerve impulses which may have electrochemical consequences in the brain, additional to the consequences of peripheral nociceptive input[38]. Evidence suggests that experimentally induced psychosocial stress (e.g. 'the Trier Social Stress test') can contribute to central sensitization[48]. Also, negative cognitive-affective reactions to pain, such as pain catastrophizing, may contribute to central sensitization and increased pain sensitivity[49,50]. These negative affective reactions have been found to increase brain activity in regions related to attention to pain, emotion and motor activity[49]. One recent study examined brain activation of fibromyalgia patients in response to negative, positive and neutral picture presentation[51]. Remarkably, fibromyalgia patients, unlike controls, did not perceive painful stimuli in the presence of positive pictures as less painful than those received while looking at neutral pictures, and pain was rated almost just as painful as during negative picture presentation. This was reflected by reduced activity in the orbitofrontal cortex (control/emotion) and the ventral anterior cingulate cortex (affect/pain modulation). Chronic pain patients may thus show a deficient connection of positive emotions with pain[51].

Although not examined in this thesis, brain alterations might explain the link between negative experiences and the onset of chronic pain. From acute to chronic pain, there seems to be a shift in involvement of pain-modulatory brain areas to emotion-related brain areas[52]. Pain is sensory information that needs to be evaluated by the central nervous system, a complex process which involves memory, reasoning, and emotional processes[38,46]. Several neuroimaging studies have shown that life stress was associated with structural and functional alterations in brain regions related to cognitive and emotional functioning[25]. Similar brain regions seem to play a role in chronic pain, such as the dorsolateral and medial pre-frontal cortex, the anterior cingulate cortex and the insula[25,53]. In addition, chronic pain subjects have shown accelerated gray matter loss, indicative of premature aging[54]. Nevertheless, a major caveat of the current literature is its failure to identify whether these brain alterations occur before or after the development of chronic pain[55]. Thus,

although brain changes might modulate between stressful events and chronic pain, more prospective studies need to be performed to shed light on this hypothesis. One large-scale study (n=2987) suggests that genetic factors were at least just as important as environmental factors in the development and severity of chronic pain[56]. That study found an heritability estimate of 30% for severe chronic pain (Grade III and IV on the Chronic Pain Grade questionnaire)[56]. It is most likely that a combination of (epi)genetic factors, vulnerability to an altered stress response, life stress and impaired descending pain modulation underlies the etiology of chronic pain[25,55,57]

Although we cannot provide a definite answer to the question how stressful events can induce chronic pain, the current biopsychosocial perspective on chronic pain suggests that thought processes can be powerful enough to contribute to chronic pain[38]. Nevertheless, the field of psychosocial stress and chronic pain is a complicated one and the precise dynamics remain to be further elucidated.

Different predictors for onset vs. persistence of chronic pain

This thesis shows that predictors associated with *the onset* of chronic pain were different from predictors of *the persistence* of chronic pain. Our study found that life events, but not biological stress systems were predictors of chronic pain onset (Chapter 4). Remarkably, neither life events nor biological stress systems seemed to play a role in the persistence of chronic pain (Chapter 5).

Stressful life events appeared to play a role in the transition from acute to chronic pain rather than from chronic pain to persisting chronic pain. This is in contrast to the idea that psychosocial stress triggers both the development and worsening of central sensitization[6]. Our data implies that biological alterations occur in a later phase, possibly as a consequence of the chronic stressor of ongoing pain. These biological changes and the experience of negative life events do not seem to further determine whether a person's chronic pain persists. Beyond this thesis, longitudinal studies examining these associations are currently lacking. However, previous studies did focus on other determinants and found that sociodemographic, pain-related, sleep-related, somatic and psychosocial factors may determine chronic pain persistence[58-62].

Two previous large-scale prospective studies (n>19.000) also showed other predictors for the onset (obesity, sleep problems, chronic disease[63]) than for the persistence (anxiety/depression, smoking, body mass index, sleep problems, age and gender[64]) of chronic widespread pain over 11 years follow-up. This seems to be in line with evidence from psychiatric research. For example, one previous cross-sectional study suggests that biological stress systems and BDNF play a role in the etiology but not in the progression from first to subsequent episodes of major depressive disorder (MDD)[65]. Thus, these studies, in combination with our findings, seem to underline that there are different risk factors for a different stage of the illness.

Biological stress systems in chronic pain vs. psychopathology

The co-occurrence of chronic pain and psychopathology seems to be more the rule than the exception[66,67]. Chronic pain seems to increase the risk of the onset and worsen the course of depression and anxiety[68,69]. Reversely, depression and anxiety can increase the risk of the onset and persistence chronic pain[63,64]. It has even been hypothesized that chronic pain and psychiatric disorders are manifestations of the same underlying pathophysiological condition, as they are both characterized by 'neurosensitization'[70] and share similar neuroendocrine, immune and autonomic disturbances of the stress response[6,71].

Overall, this thesis showed that depression and anxiety seemed to influence our associations between biological factors and chronic pain. Depressive and anxiety disorders, typically related to hypercortisolemia, appeared to mask the association between hypocortisolemia and chronic pain (Chapter 2). Several previous studies that failed to stratify their analyses according to the presence of psychopathology might have led to misconceptions regarding the role of the HPA axis in chronic pain. It could be that different subtypes of depression are related to distinct biological changes. For example, hypercortisolemia has particularly been found in melancholic depression, but not in atypical depression[72]. This thesis also showed that adjusting for depression and anxiety moderately attenuated the cross-sectional associations of the immune system with chronic pain (Chapter 3). In addition, we found unaltered BDNF serum levels in chronic pain (Chapter 6), whereas a previous NESDA study found decreased BDNF serum levels in depression[73]. Whereas hypocortisolemia did not seem to play a role in the course of chronic pain (Chapter 5), it has previously been related to the course of depression[74]. Thus, although similar stress systems might be involved, our studies suggest that chronic pain and psychopathology may not be entirely similar in their underlying pathophysiology.

A new hypothesis for the etiology of chronic pain

Based on the overall findings of this thesis, I propose a new hypothetical framework (see Figure 1) in which psychosocial stress factors and sleep problems induce central sensitization, ultimately resulting in the onset of chronic pain, which subsequently alters function of biological stress systems (hypocortisolemia, higher innate immune response). These biological alterations, and adverse life events, do not further impact the persistence of chronic pain (not depicted in Figure 1). In addition, other factors, not examined in this thesis, such as genetic[55,56] and other biological[6] and psychosocial factors[75] presumably play a role in the etiology of chronic pain.

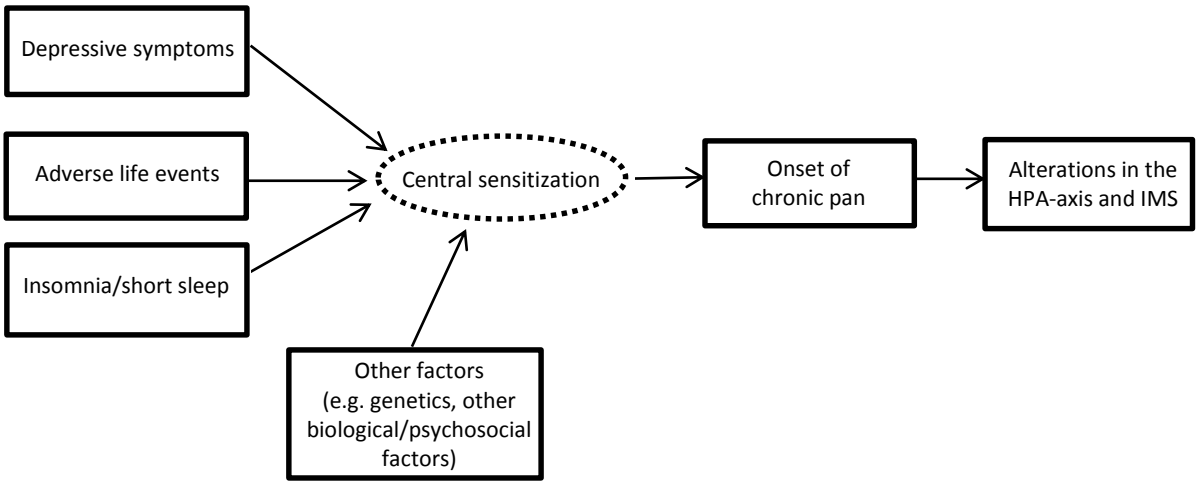

Figure 1. New hypothetical framework for the etiology of chronic pain based on findings in this thesis.

Methodological considerations

Strong aspects of the NESDA study are the large sample size, the longitudinal design, the assessment of a wide range of biological variables, and the possibility to take several relevant covariates into account. The NESDA study included subjects with a great variation in symptoms, with or without depressive or anxiety disorders, which resulted in the inclusion of sufficient subjects both with and without the presence, onset and persistence of chronic pain. Moreover, we had sufficient sample sizes when stratifying our analyses, which provided the opportunity to examine moderation effects of variables such as depression.

However, with every large-scale cohort study, there are some methodological aspects to consider. Overall, one consideration is our measurement of chronic pain, which is distinct from previous studies. Our classification of chronic multi-site musculoskeletal pain is pain in the extremities, the back, and the neck in the prior 6 months. This seems to be a broader approach compared to previous studies using clinical examination of the chronic widespread pain (CWP) criteria (pain in all four body quadrants)[76]. Thus, subjects in the NESDA study may show milder pain complaints than subjects from previous studies that used these CWP criteria. It is possible that our results may systematically vary between individuals and between patients with pain who are given different diagnoses (fibromyalgia (CWP), rheumatoid arthritis, osteoarthritis or low back pain). However, multi-site pain not meeting the CWP criteria can be just as demanding and limiting in daily life[77]. Moreover, since contaminations across diagnoses is not uncommon in clinical reality, setting broader parameters for studying chronic pain may be useful.

Due to the design of the NESDA study, we included a high rate of participants with depressive and/or anxiety disorders. This may have resulted in selection bias; our participants may not

adequately represent the general population. Nonetheless, certain levels of psychosocial stress at baseline are needed to be able to include sufficient persons with chronic pain. Also, the NESDA study enabled us to take the confounding or moderating effects of psychopathology into account, which were measured by structural interviews according to Diagnostic and Statistical Manual (DSM) standards[78]. This is a major strength compared to previous studies on chronic pain, which mostly used self-report questionnaires to measure depression and anxiety, if they included it as confounders at all.

Another important issue is the measurement of biological variables. First, whereas missing data does not seem differential between persons with and without chronic pain for the innate immune response, it may be slightly differential for salivary cortisol. Since participants collected cortisol levels at home, the levels may be subject to differences due to compliance with the sample protocol. Although our previous pilot study indicated that NESDA participants were compliant with the intake of dexamethasone[79], missing data may still be differential for the basal cortisol levels. Second, we assessed biological factors on 1 day, whereas levels of cortisol, cytokines, autonomic markers and BDNF may fluctuate from day to day. This may have affected the reliability of our findings. Inflammatory markers have been found to accurately capture the short-term variability up to 6 months within an individual[80]. Most of the variance for cortisol, however, may reflect day-to-day fluctuation[81]. It has been suggested that assessment of 2 to 6 days can substantially increase the reliability of the cortisol awakening response[82]. However, costs and burden of participants also play a role in our large epidemiological study, and we have likely compensated the reliability of our findings with our large sample size. Third, this thesis assessed biological stress systems at a peripheral level, and these may not be correlated with levels of the same marker within the central nervous system. For example, a higher innate immune response was found in blood plasma of chronic pain subjects, but this does not provide any information on immune processes within their brain and spinal cord. It may be relevant to examine whether biological vulnerability for central sensitization can be found when examining central processes. On the other hand, pain hypersensitivity might be mainly central, but the combination of peripheral impulse input and increased central pain sensitivity is thought to be responsible for chronic pain disorders[83,84]. This suggests to study the relative contribution of both peripheral and central factors to chronic pain[85].

Clinical implication

The prevalence of chronic pain is increasing world-wide and holds a top position among the list of diseases with high disease burden[1]. In order to improve treatment, it is essential to increase our

understanding of the risk factors of the onset and persistence of chronic pain. This thesis aimed to examine several biological and psychosocial factors in relation to chronic pain.

In order to find interventions to prevent chronic pain, our findings suggest to focus on coping with stressful events and the improvement of sleep and depressive symptoms. Studies targeting these factors for prevention of chronic pain are currently lacking. One recent Cochrane review suggests that cognitive behavioral therapies aimed at decreasing distress may provide small benefits for reducing pain, negative mood, and disability in fibromyalgia patients[86]. Interventions based on changing sleeping habits may also improve pain and mood[60,87].

When subjects have already been exposed to chronic pain, stress reduction programs might also positively affect the biological changes (hypocortisolemia, higher innate immune response) that we found in our chronic pain subjects. Although evidence is suggestive, some previous studies found that treatment aimed at reducing arousal and stress (e.g. meditation, mindfulness stress-based therapy) can have a beneficial effect on immune and cortisol parameters[88-90]. This could possibly result in normalization of the biological stress response, which might subsequently improve pain symptoms.

This thesis found that biological stress systems and life events did not play a role in the persistence of chronic pain. This suggests future research is needed to determine targets for treatment of chronic pain. One previous cohort study among Dutch chronic widespread pain patients (n=200) found that baseline predictors of better outcome of multidisciplinary treatment were less anxiety, stronger beliefs in personal control, less belief in consequences, less pain, less fatigue, higher level of education, and male gender[91]. Previous studies suggested that key mechanisms of change in treatment of chronic pain could be improvement of negative emotional cognitions such as catastrophizing[92,93] and fear-avoidance beliefs (avoidant behavior of activity based on fear)[94-96].

Future research

This thesis aimed at providing insight into the factors contributing to chronic pain. Although this thesis significantly contributed to the knowledge on the role of biological and psychosocial factors in chronic pain, as with any good research, many questions still remain which can be addressed in future studies. First, this thesis can speculate that HPA axis and IMS alterations are consequences of chronic pain, but we only provided evidence that these changes are likely no causes of the condition. Additional large-scale prospective studies are needed to confirm that these biological changes are indeed consequences of chronic pain. To confirm our hypothesis, a group of subjects with chronic pain at baseline has to be identified and followed-up over time. Both at baseline and follow-up, biological function, pain and several covariates such as depression should be assessed. Also, to determine

generalizability of these findings, studies could be performed examining more severe types of pain, such as chronic widespread pain, the cardinal symptom of the fibromyalgia syndrome.

Second, future studies could focus on examining which pathway explains the associations for adverse life events, disturbed sleep and depressive symptoms with the future onset of chronic pain. Biological stress reactivity in response to stress rather than basal activity could be examined as such a potential pathway. The reactivity of (neuro)biological factors should be assessed at the peripheral as well as the central level of the nervous system to examine their relative contribution to chronic pain. Neuroimaging studies could be performed to examine brain activity in emotion-related areas before and after the development of chronic pain, to be able to draw conclusions about a causal direction.

Third, our findings suggest to test a prevention program that includes coping with stressful events and improvement of sleep and depressive symptoms, in order to prevent the development of chronic pain. This treatment could be tested in subjects that are vulnerable for the development of chronic pain, for example subjects with a diagnosis of (another) chronic condition or acute pain patients (e.g. after surgery). Finally, this thesis further suggests to examine predictors of chronic pain persistence, other than biological stress systems and life events, to be able to identify which persons are at risk for ongoing pain while other persons improve in their pain symptoms. Future studies could assess the persistence of chronic pain over a longer course of time than 6 years, in particular because most patients ending up in a clinical setting have had pain symptoms for a longer period than 6 years[92,97].

In conclusion

This thesis could not confirm that dysfunction of three major biological stress systems –HPA axis, IMS and ANS– are associated with the development of chronic pain. Chronic pain subjects did show altered HPA axis and IMS function in our cross-sectional studies, suggesting these changes might evolve as consequences of chronic pain. Biological stress systems and adverse life events do not further impact the persistence of chronic pain. Adverse life events, disturbed sleep and depressive symptoms are all independent risk factors of future development of chronic pain. These psychosocial factors could be valuable targets for prevention of chronic pain among those at risk for developing the condition. In addition, future large-scale prospective studies should be performed to test our hypothesis that changes in HPA axis and IMS function are indeed consequences of chronic pain.

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